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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/584,877	06/29/2006	Qiang Yu	09548.1035USWO	7935

52835 7590 01/26/2009

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EXAMINER	
JEAN-LOUIS, SAMIRA JM	

ART UNIT	PAPER NUMBER
1617	

MAIL DATE	DELIVERY MODE
01/26/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/584,877	YU ET AL.	
	Examiner	Art Unit	
	SAMIRA JEAN-LOUIS	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) *8-10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *06/29/06, 08/18/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Claims 1-10 are currently pending in the application.

Applicant's election of Group II (i.e. method of treating or preventing arthritis) and election of the compound of formula II and request for rejoinder in the reply filed on 11/19/08 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Thus, the requirement is deemed proper and is therefore made FINAL.

Claims 8-10 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected group and species, there being no allowable generic or linking claim.

Priority

Acknowledgment is made of applicant's claim for foreign priority. It is noted, however, that applicant has not provided English translation of the Chinese application as required by 35 U.S.C. 119(b). Nonetheless, the priority date of the instant invention is December 30, 2003. Without the English translation, one cannot ascertain if the instant invention is present in the Chinese application. Therefore, art prior to the PCT date, but not before the date of the Chinese application may be cited against the claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for the treatment of arthritis, does not reasonably provide enablement for a method for the prevention of arthritis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Importantly, given that the term "prevention" implies an absolute term, it is assumed that no known disease can be absolutely prevented at this time especially those resulting from genetic impairment. In fact, Barton et al. teach that genetic factors contribute greatly to the etiology of rheumatoid arthritis, a subtype of arthritis. Moreover, applicant does not reasonably provide enablement for the prevention of arthritis nor does the application enable any person skilled in the art to use the invention for preventing arthritis as recited in these claims.

The instant claims are drawn to a method for the treatment of arthritis comprising administering to a patient a coumestans compound of formula I or pharmaceutically acceptable salts thereof, or an extract containing the coumestans compound of formula

I or pharmaceutical acceptable salts thereof. The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention.

Attention is directed to *In reWands,* 8USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman,* 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

1. The nature of the invention, state and predictability of the art, and relative skill level

The instant invention pertains to a method for the treatment of arthritis comprising administering to a patient a coumestans compound of formula I or pharmaceutically acceptable salts thereof, or an extract containing the coumestans compound of formula I or pharmaceutical acceptable salts thereof. The relative skill of those in the art is high, that of an MD or PHD. That factor is outweighed, however, by the unpredictable nature of the art. The skilled artisan would view that the prevention of arthritis in an individual totally, absolutely, or permanently, is highly unlikely given that genetic factors cannot be avoided and consequently such genetic influences would necessarily result in the occurrence of arthritis.

2. The breadth of the claims

The claims are thus very broad insofar as they recite the "prevention" arthritis, i.e., the complete prevention of same. While such "prevention" might theoretically be possible under strictly controlled laboratory conditions, as a practical matter it is nearly impossible to achieve in the "real world" in which patients live.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no direction or guidance for preventing arthritis by administering a compound of formula I or a pharmaceutically acceptable salt thereof to a patient. In fact, applicant provided no guidance or working examples as to how to prevent arthritis using a compound of formula I. Note that lack of a working example, is a critical factor to be considered, especially in a case involving an unpredictable and underdeveloped art. See MPEP 2164.

4. The quantity of experimentation necessary

Because of the known unpredictability of the art, and in the absence of experimental evidence, no one skilled in the art would accept the assertion that the instantly claimed compounds of formula I could be predictably used to prevent arthritis as inferred by the claim and contemplated by the specification. Accordingly, the instant claims do not comply with the enablement requirement of §112, since to practice the

invention claimed in the patent a person of ordinary skill in the art would have to engage in undue experimentation in order to determine if said compounds of formula I claimed by applicant can in fact prevent arthritis, with no assurance of success.

Genentech, 108 F.3d at 1366 states that " a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, method for the prevention of arthritis comprising administering to a patient a coumestans compound of formula I or pharmaceutically acceptable salts thereof, or an extract containing the coumestans compound of formula I or pharmaceutical acceptable salts thereof is not considered to be enabled by the instant specification.

The claims are examined herein for a method for the treatment of arthritis comprising administering to a patient a coumestans compound of formula I or pharmaceutically acceptable salts thereof, or an extract containing the coumestans compound of formula I or pharmaceutical acceptable salts thereof.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1 and 3-7 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Kobori et al. (Cell Death and Differentiation, Oct. 3, 2003, published online, Vol. 11, pgs. 123-130).

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Kobori et al. teach that wedelolactone (i.e. applicant's elected species) has been identified as a coumestan contained in E. prostrate L. and was suggested to be the

active component of this herb (see pg. 128, left col., Discussion and pg. 124, left col. paragraph 2). Kobori et al. also demonstrated that wedelolactone has anti-inflammatory effect through inhibition of IKK activity and caspase-11 expression (see pg. 128, left col. and right col. line 1). In fact, Kobori et al. teach that wedelolactone was able to inhibit the secretion of pro-inflammatory cytokine IL-1ß, which is maturated by caspase-11 activated caspase 1 (see pg. 128, right col., lines 1-3). Moreover, Kobori et al. teach that due to the ability of wedelolactone to inhibit the activation of NF-kB pathway, such compound provides an interesting potential lead compound in anti-inflammatory therapy in diseases such as rheumatoid arthritis (see pg. 128, right col., paragraph 2). Additionally, Kobori et al. teach that isolating wedelolactone from E. prostrate L. wherein the dried entire plants were homogenized in ethanol with a blender (see pg. 129, left col., paragraph 3). The ethanol extract is then filtered and the supernatant of the filtrate is then concentrated by evaporation and then washed with hot water (see pg. 129, left col., paragraph 3). The hot water fraction was partitioned with ethyl acetate and the ethylacetate fraction was concentrated by evaporation. The dried ethylacetate fraction was dissolved in ethanol and further fractionated to result in a precipitate. The precipitate was then washed several times, dissolved in a small amount of DMSO and recrystallized in ethanol. The precipitate and the wedelolactone were separated and identified by UV spectrum, MS spectra (see pg. 129, left col., Isolation of wedelolactone from *E. prostrata L).*

Kobori et al. do not specifically teach that the method of obtaining the aforementioned compound (i.e. wedelolactone) involves eluting the precipitate on a silica gel column with gradients of petroleum ether/acetone mixture or dichloromethane/acetone mixture or a toluene/acetone/formate mixture. Similarly, Kobori et al. do not teach a method of treating arthritis.

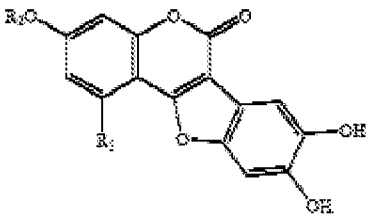
Kobori et al. however do teach that wedelolactone which comes from the extract of *E. prostrata L.* is a potential compound in the treatment of anti-inflammatory diseases including rheumatoid arthritis. Moreover, Kobori et al. teach that the aforementioned compound can be extracted from the entire plant, filtered, concentrated, and washed with hot water which necessarily reads on applicant's claim limitation of water temperature of 50-80 °C. While Kobori et al. is silent on elution of the precipitate using petroleum ether/acetone mixture, dichloromethane/acetone mixture, or a toluene-acetone-formate mixture, it is the Examiner's contention that the resulting precipitate of the prior art is substantially the same as that of applicant regardless of the type of elution solvents utilized. Consequently, a *prima facie* case of obviousness has been established. In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977).

Thus, to one of ordinary skill in the art at the time of the invention would have found it obvious to utilize the wedelolactone compound of Kobori et al. to treat rheumatoid arthritis since Kobori et al. teach that wedelolactone is a potential compound in the treatment of anti-inflammatory disease including rheumatoid arthritis. Given the

teachings of Kobori et al., one of ordinary skill would have been motivated to utilize the compound of Kobori et al. to treat rheumatoid arthritis as taught by Kobori et al. with the reasonable expectation of providing a method that is efficient in treating rheumatoid arthritis and other inflammatory diseases.

Claims 1-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yuan et al. (U.S. 6,552,071 B2, cited by applicant and filed on an IDS 1449) in view of Matsui et al. (Exp. Opin. Theur. Targets, 2003, Vol. 7, No. 6, pgs. 701-724).

Yuan et al. teach methods and compounds for treating inflammation (see abstract and col. 1, lines 13-15). The methods involve the use of the plant extract wedelolactone or comprise administering wedelolactone or a salt thereof to a subject (see col. 1, lines 43-46 and 55-62). Particularly, Yuan et al. teach a method of treating inflammation in a subject involving administering in a pharmaceutically acceptable carrier a compound having the formula:



where R1 is OH and R2 is CH3 (see col. 2, lines 18-36 and 59-64). Yuan et al. further teach that by plant extract, it is meant that a compound of mixture of compounds that are obtained from a plant may be used after obtaining such mixture by chopping the entire plant into small pieces, treating the plant with high pressure, distilling the plant or

treating the plant with solvent and further teach the use of *Eclipta prostrate L.* extract as responsible for inhibiting pro-inflammatory cytokines such as caspase-11 and which contains wedelolactone (see col. 4, lines 24-29, 55-58 and example 3). Yuan et al. further teach extraction of Eclipta prostrate L. with ethanol followed by concentration through evaporation (see col. 11-12, example 2). The dried ethanol extract was next washed with boiling water which necessarily reads on applicant's claim limitation of a boiling temperature of 50-80 °C since such temperature render obvious the fact that the water would be boiling. The boiling water was then partitioned with ethyl acetate and the ethyl acetate fraction which contains the active ingredient (i.e. wedelolactone) was further purified by silica gel chromatography and preparative high pressure liquid chromatography (HPLC) and components identified using thin layer chromatography (see col. 12-13, example 4). Yuan et al. importantly teach that the ethanol extract fraction and the boiling water extract both contain wedelolactone which suppress the expression of caspase-11 (see col. 13, lines 22-23).

Yuan et al. do not specifically teach that the method of obtaining the aforementioned compound (i.e. wedelolactone) involves eluting the precipitate on a silica gel column with gradients of petroleum ether/acetone mixture or dichloromethane/acetone mixture or a toluene/acetone/formate mixture. Similarly, Yuan et al. do not teach a method of treating arthritis.

Yuan et al. however do teach that wedelolactone which comes from the extract of *E. prostrata L.* is a potential compound in the treatment of anti-inflammatory diseases including rheumatoid arthritis. Moreover, Kobori et al. teach that the aforementioned compound can be extracted from the entire plant, chopped into pieces, concentrated, and washed with boiling water which necessarily reads on applicant's claim limitation of water temperature of 50-80 °C. While Yuan et al. is silent on elution of the precipitate using petroleum ether/acetone mixture, dichloromethane/acetone mixture, or a toluene-acetone-formate mixture, it is the Examiner's contention that the resulting precipitate of the prior art is substantially the same as that of applicant regardless of the type of elution solvents utilized. Consequently, a *prima facie* case of obviousness has been established. In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). Moreover, given that Yuan et al. teach the salts of wedelolactone, the Examiner contends that such term render obvious applicant's disclosed salts in claim 2.

Matsui et al. teach that Rheumatoid arthritis (RA) is a common chronic inflammatory joint disease with destruction of the cartilage and bone. RA is characterized by the intensively proliferating synoviocytes and the dense infiltration of various types of activated immune competent cells (see pg. 708, left col.). Matsui et al. further teach that RA patients possess aberrant T cells which react with collagen type II autoantigens which have been found to induce inflammatory arthritis in mice (see pg. 709, left col., paragraph 1). Importantly, Matsui et al. teach that cytokines and

chemokines are involved in the development of RA and that RA patients tend to show an increase in pro-inflammatory cytokines (see pg. 709, left col., paragraph 2).

Thus, to one of ordinary skill in the art at the time of the invention would have found it obvious to utilize the wedelolactone compound or plant extract of wedelolactone of Yuan et al. to treat rheumatoid arthritis since Yuan et al. teach that wedelolactone is effective against inflammation and Matsui et al. teach that Rheumatoid arthritis is an inflammatory disease characterized by infiltration of inflammatory cytokines. Given the teachings of Yuan and Matsui, one of ordinary skill would have been motivated to utilize the compound or extract of Yuan et al. to treat rheumatoid arthritis as taught by Matsui et al. with the reasonable expectation of providing a method that is efficient in treating rheumatoid arthritis and other inflammatory diseases.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samira Jean-Louis whose telephone number is 571-270-3503. The examiner can normally be reached on 7:30-6 PM EST M-Th.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/S. J. L. /

Examiner, Art Unit 1617

01/15/2008

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1617